Journal of the American College of Cardiology
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Published by Elsevier Science Inc.

Vol. 36, No. 2, 2000
ISSN 0735-1097/00/$20.00
PII S0735-1097(00)00727-0

Responses to Constant Work Rate Bicycle Ergometry Exercise in Primary Pulmonary Hypertension: The Effect of Inhaled Nitric Oxide

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OBJECTIVES The purpose of this study was to investigate the responses of patients with primary pulmonary hypertension (PPH) to constant work rate exercise and to examine the effect of nitric oxide (NO) inhalation.

BACKGROUND Maximal exercise tolerance is reduced in PPH, but gas exchange responses to constant work rate exercise have not been defined. We hypothesized that increased pulmonary vascular resistance in PPH would reduce the rate of rise of minute oxygen consumption in response to a given work rate. Because NO may lower pulmonary vascular pressures in PPH, we also postulated that inhaled NO might ameliorate gas exchange abnormalities.

METHODS Nine PPH patients and nine matched normal subjects performed 6-min duration constant work rate cycle ergometry exercise (33.9 ± 13.4 W). Patients performed two experiments: breathing air and breathing air with NO (20 ppm). Preexercise right ventricular systolic pressure was assessed by Doppler echocardiography. Normal subjects performed the air experiment only. Gas exchange and heart rate responses were characterized by fitting monoexponential curves.

RESULTS In PPH patients, resting right ventricular systolic pressure fell after NO inhalation (from 83.8 ± 16.9 to 73.9 ± 21.6 mm Hg, $p < 0.01$, analysis of variance with Tukey correction), but not after breathing air alone (from 88.0 ± 20.8 to 86.7 ± 20.6 mm Hg, p = NS). Nitric oxide did not affect any of the gas exchange responses. Minute oxygen consumption was similar by the end of exercise in patients and normals, but increased more slowly in patients (mean response time [MRT]: air, 63.17 ± 14.99 s; NO, 61.60 ± 15.45 s) than normals (MRT, 32.73 ± 14.79, $p < 0.01$, analysis of variance, Tukey test). Minute oxygen consumption kinetics during recovery were slower in patients (MRT air: 82.50 ± 29.94 s; NO, 73.36 ± 15.87 s) than in normals (MRT, 34.59 ± 7.11 s, $p < 0.01$). Heart rate kinetics during exercise and recovery were significantly slower in patients than in normals.

CONCLUSIONS The cardiac output response is impaired in PPH. Nitric oxide lowered pulmonary artery pressure at rest, but failed to improve exercise gas exchange responses. (J Am Coll Cardiol 2000;36:547–56) © 2000 by the American College of Cardiology

In patients with primary pulmonary hypertension (PPH), the initial symptoms are usually related to exertion and this is reflected in reduced maximal O_2 consumption ($\dot{V}O_{2max}$) on incremental maximal exercise testing (1,2). Submaximal exercise testing has also been advocated as a means of assessing patients with exercise intolerance. Compared with maximal exercise testing, it is more representative of daily activity and may be less unpleasant for the patient. In patients with chronic heart failure due to left ventricular disease, minute oxygen consumption ($\dot{V}O_2$) has been found to rise more slowly than normal in response to the same constant work rate submaximal exercise (3,4). Sietsema (5) studied a group of patients with pulmonary vascular disease of mixed etiology performing submaximal exercise and again found prolonged $\dot{V}O_2$ kinetics. Casaburi et al. (6) studied a group of patients with complete heart block who had programmable permanent pacemakers. They found that $\dot{V}O_2$ rose more quickly in response to the same submaximal work rate if the pacemaker rate was increased. The pattern of decline in $\dot{V}O_2$ after cessation of exercise also appears to be abnormally slow in patients with chronic heart failure (4,7), but little is known about the recovery phase in PPH. If $\dot{V}O_2$ kinetics are slowed in response to exercise, the O_2 deficit is, by implication, increased. Excess postexercise O_2 consumption (EPOC), often referred to as the O_2 debt, may be elevated as a consequence, although the link between O_2 deficit during exercise and EPOC has been questioned (8).

Vasodilator drugs have been the mainstay of treatment in PPH. Nitric oxide (NO) has shown some promise as a potential therapy. The problem of rapid inactivation of NO by hemoglobin (9) may be circumvented by inhalation of NO gas so that it reaches the resistance pulmonary arteries abluminally. Its subsequent inactivation on reaching the

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Manuscript received May 17, 1999; revised manuscript received February 1, 2000, accepted March 30, 2000.

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August 2000:547–56

Abbreviations and Acronyms

EPOC = excess postexercise oxygen consumption
LAT = lactic acidosis threshold
MRT = mean response time
NO = nitric oxide
PCr = phosphocreatine
PPH = primary pulmonary hypertension
RVSP = right ventricular systolic pressure
S_pO_2 = hemoglobin saturation measured by pulse oximetry
$\dot{V}CO_2$ = minute carbon dioxide production
$\dot{V}E$ = minute ventilation
$\dot{V}O_2$ = minute oxygen consumption

circulation eliminates systemic arterial effects (10,11). Using invasive techniques, previous investigators have found an acute beneficial effect on pulmonary vascular resistance after inhalation of NO in PPH (10,12). Hemodynamic changes are, however, not necessarily correlated with clinical improvement in PPH (13) or chronic heart failure (14). The use of exercise testing may provide information complementary to hemodynamic measurements (14).

The purpose of the current study was twofold: 1) to characterize the responses to constant work rate exercise in a group of patients with PPH compared with a group of normal subjects, and 2) to test the hypothesis that the acute administration of inhaled NO as an add-on to current therapy would improve abnormal exercise responses in PPH.

METHODS

Subjects. Six women and three men with clinically stable PPH were studied. The mean duration of disease was 29.3 months (range 5.4–94.3 months). All but one had previously undergone right heart catheterization that showed severe elevation of pulmonary arterial pressures (Table 1). One patient had been found to have arterial desaturation at rest while at an altitude of 8,000 feet and accordingly had left atrial, pulmonary venous and femoral arterial blood sampling performed at the time of catheterization. She was found to have a patent foramen ovale, and a step-down in O_2 saturation between pulmonary venous blood and systemic arterial blood suggested a right-to-left shunt across the patent foramen ovale. None of the patients had evidence of pulmonary embolism on isotope perfusion lung scanning. All patients were taking one or more drugs for their disease. Seven patients were being treated with continuous intravenous infusions of prostacyclin (Flolan; Glaxo Wellcome, Research Triangle Park, North Carolina) at a mean dose of 8.7 ng/kg/min (range 3–20 ng/kg/min) and five were being treated with diuretics at a mean dose of furosemide of 44 mg (range 20–80 mg). Four patients were taking calcium channel antagonists and five were taking digoxin. Drug therapy was stable for 2 months before the study and for the duration of the study period. All had tricuspid regurgitation identifiable by echocardiography.

Nine healthy subjects were recruited. These subjects were individually matched for age and gender with the PPH patients. All were active but did not participate in regular training programs.

Ethical approval for the study was granted by the Harbor-UCLA Human Subjects Committee. Written informed consent was given by all subjects. Characteristics of the subjects are summarized in Table 1.

Experimental protocol. All exercise tests were performed on an electronically braked cycle ergometer (Quinton Corival, Seattle, Washington). In five of the patients who had long distances to travel, all tests were completed on the same day separated by at least 2 h. In the other four patients, tests were performed at weekly intervals.

PRELIMINARY INCREMENTAL EXERCISE TEST. Subjects were familiarized with the apparatus and performed a continuous incremental symptom-limited maximal test for determination of $\dot{V}O_{2max}$ and lactic acidosis threshold (LAT) (Table 1). The incremental work rate was set at 20 W/min in the normal subjects. In the PPH patients, the probable exercise tolerance was estimated from the clinical

Table 1. Subject Characteristics and Constant Work Rates Performed

	PPH Patients	Normal Subjects
Age (yr)	34.9 ± 6.7	34.1 ± 6.1
Weight (kg)	73.6 ± 14.7	70.1 ± 10.5
Height (m)	1.70 ± 0.08	1.70 ± 0.07
Hemoglobin (g/dl)	15.7 ± 2.2	14.0 ± 1.3
Systolic pulmonary arterial pressure at right heart catheterization (mm Hg)	96 ± 28 (n = 8)	—
Diastolic pulmonary arterial pressure at right heart catheterization (mm Hg)	44 ± 14 (n = 8)	—
Peak work rate (W)	61 ± 22	196 ± 50
$\dot{V}O_{2max}$ (liters/min)	1.00 ± 0.22	2.41 ± 0.75
LAT (liters/min)	0.73 ± 0.17	1.32 ± 0.35
Constant work rate (W)	33.9 ± 13.4	33.9 ± 13.4

Data are mean ± SD. Pulmonary artery pressure was measured at right heart catheterization, which was performed during the initial evaluation and not at the time of the exercise study.

LAT = lactic acidosis threshold; PPH = primary pulmonary hypertension; $\dot{V}O_{2max}$ = maximal oxygen consumption, measured during symptom-limited maximal exercise.

history. Based on this estimate, a work rate increment of either 5 or 10 W/min was individually chosen to prevent excessively short or long test durations (15). All subjects were instructed to stop exercise immediately if they experienced dizziness or chest pain. From the test performed by each PPH patient, a work rate was determined that corresponded to the $\dot{V}O_2$ at the LAT plus 30% of the difference between the LAT and $\dot{V}O_{2max}$, i.e.: ($\dot{V}O_2$ at LAT) + $0.3(\dot{V}O_{2max} - (\dot{V}O_2$ at LAT)). This individualized work rate (Table 1) was used for each patient-control matched pair when performing the constant work rate tests described below.

CONSTANT WORK RATE EXERCISE TESTS. Each patient subsequently performed two constant work rate tests (second and third tests). A Teflon cannula was inserted into an antecubital vein for measurement of peripheral venous lactate concentrations. The patient then rested, seated on the bicycle ergometer. An echocardiogram was performed for estimation of right ventricular systolic pressure (RVSP) by Doppler. Echocardiography was performed by the same operator throughout the study. After the echocardiogram, the subject began breathing a gas mixture from a large (140-liter) breathing bag. The gas mixture was compressed air mixed, using a blender (Bird Instrument Corp., Palm Springs, California), with either N_2 or NO 400 ppm in N_2 (Air Liquide, Downey, California). The ratio of compressed air to either of the other gases was kept constant at 20:1 so as to obtain NO concentrations of 20 ppm in the breathing bag. The control situation with pure N_2 was needed to ensure that the small drop in F_iO_2 was the same in both tests. The F_iO_2 was measured continuously at rest and during exercise by mass spectrometry (see below). In addition, the F_iNO was measured continuously throughout the NO study using an NO analyzer (Dasibi Environmental, Glendale, California) to ensure that it did not vary. After 15 min of breathing the gas mixture, the echocardiogram was repeated. The order in which the two gas mixtures were breathed was randomized. The patient and echocardiographer were not told which gas mixture was being breathed. After breathing the gas mixture for a total of 25 min, the patient performed a 6-min duration constant work rate test, followed by 10 min of recovery. The patient continued to breathe the relevant gas mixture throughout. The patient began to pedal at the designated work rate immediately from rest. The work rate was the same for the two tests in any one individual. The two constant work rate tests when carried out on the same day were separated by a minimum of 3 h.

The normal subjects performed only one constant work rate test at the same absolute work rate as the patient with whom they were individually matched (see preceding text and Table 1). Echocardiography was not performed. The gas mixture was breathed from the breathing bag as above, but only the compressed air/N_2 mixture was used.

Gas exchange measurements. The nose was occluded by a nose clip and subjects breathed through a mouthpiece, attached to a volume turbine transducer (Alpha Technologies, Laguna Niguel, California) for determination of inspired and expired volumes. Gas samples were drawn continuously from a side port of the mouthpiece for analysis of fractional concentrations of O_2, CO_2 and N_2 by a mass spectrometer (Perkin-Elmer, Oakbrook, Illinois). The analog signals from the turbine and mass spectrometer were digitized at a resolution of 50 Hz and read into a PC. Breath-by-breath values of minute ventilation ($\dot{V}E$), $\dot{V}O_2$ and CO_2 production ($\dot{V}CO_2$) were calculated as previously described (16).

Echocardiography. Echocardiography was performed using a phased array ultrasound machine with a 2.5-MHz transducer (Acuson, Mountain View, California). Parasternal and apical images were obtained with color flow Doppler to align the continuous-wave Doppler cursor with the tricuspid regurgitant jet. The RVSP gradient was estimated using the formula $\Delta P = 4\ V^2$, where ΔP is the difference between right ventricular and right atrial pressure, and V is the velocity of the tricuspid regurgitant jet (17). Right ventricular systolic pressure was calculated as ΔP + right atrial pressure. Right atrial pressure was arbitrarily assumed to be 15 mm Hg.

Analysis of data. To reduce variation in $\dot{V}O_2$ and $\dot{V}CO_2$ resulting from changes in lung volume and alveolar concentration from breath to breath, the alveolar correction of Beaver et al. (18) was employed. This method corrects the volume of O_2 and CO_2 in the alveolar gas for each breath up or down depending on changes in exhaled N_2, O_2 and CO_2 concentrations. Breath-by-breath gas exchange measurements were interpolated second-by-second. Values of gas exchange at rest were derived from the final 2 min of the resting period. Maximal exercise gas exchange was calculated from the final 30 s of the incremental exercise test. The LAT was determined by the "V-slope" method of Beaver et al. (19).

CURVE FITTING OF $\dot{V}O_2$, HEART RATE AND $\dot{V}CO_2$ RESPONSES. The $\dot{V}O_2$, heart rate and $\dot{V}CO_2$ responses obtained during the constant work rate tests were fitted to single exponential models.

A) EXERCISE. This was a single compartment exponential type model with incorporation of a variable time-delay at the beginning (Fig. 1):

$$f(t) = c + A(1 - e^{-(t-td)/\tau}),$$

where $f(t)$ represents the value of the function after t minutes of exercise, c is the preexercise value, A represents the amplitude from baseline of the asymptotic value to which the function rises, td is the delay before the exponential function commences and τ is the time constant. The longer the time constant, the slower the kinetics of the variable under consideration. Nonlinear regression analysis (BMDP statistical software package; BMDP, Los Angeles,

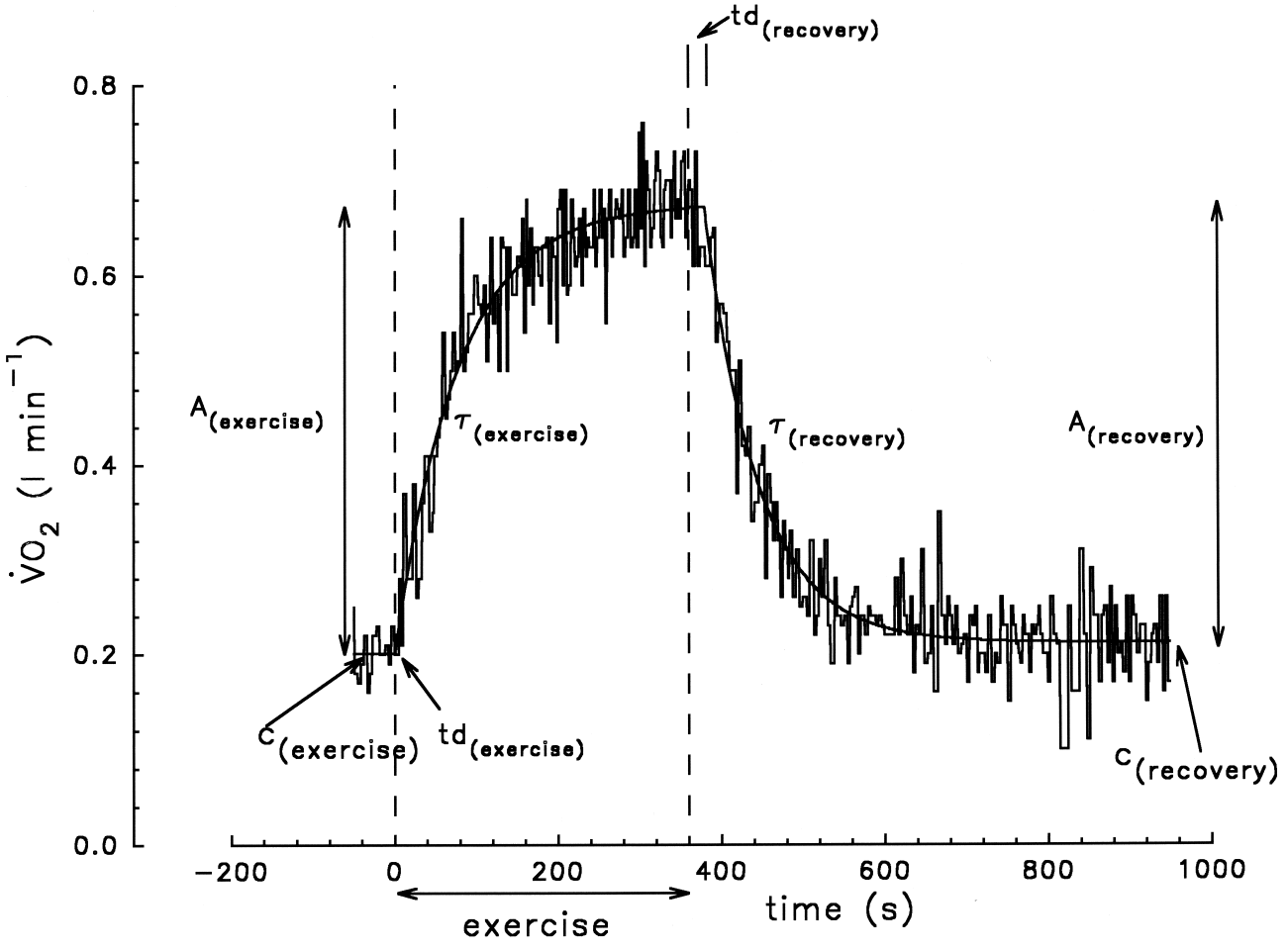

Figure 1. Data from a patient with PPH with illustration of the components of the single-exponential curves used to describe the exercise and recovery responses. In each case, the exponential function starts after a time delay. Exercise: $\dot{V}O_2 = c + A(1 - e^{-(t - td)/\tau})$, where c is preexercise baseline $\dot{V}O_2$; A is amplitude from baseline to asymptotic value; td is time delay; and τ is time constant. Recovery: $\dot{V}O_2 = c + Ae^{-(t - td)/\tau}$, where c is end-recovery asymptotic $\dot{V}O_2$; A is amplitude of response; td is time delay; and τ is time constant.

California) was used to select values for A, c, td and τ so as to achieve a minimum residual sum of squares. Mean response time (MRT) was defined as τ + td.

Previous work has suggested that a more sophisticated three-compartment exponential model may describe the rise in $\dot{V}O_2$ more precisely (20). We experimented with this model, but found that it was much more sensitive to "noise" in the data, and therefore less robust than the single exponential model.

B) RECOVERY. A single exponential model was again used:

$$f(t) = c + Ae^{-(t-td)/\tau},$$

where in this case, f(t) represents the value of the function after t minutes of recovery, c is the asymptotic value at the end of recovery, A represents the amplitude of the response, td is the delay before the exponential function commences and τ is the time constant.

OXYGEN DEFICIT AND EPOC. Oxygen deficit was derived by subtraction of the cumulative $\dot{V}O_2$ for the whole exercise period from the perceived total O_2 requirement. The average $\dot{V}O_2$ during the final 30 s of exercise was assumed to represent the $\dot{V}O_2$ appropriate to the exercise intensity. The perceived total O_2 requirement was therefore calculated by multiplying the $\dot{V}O_2$ at the end of exercise by the exercise duration (Fig. 2). Excess postexercise oxygen consumption was derived by calculating the cumulative $\dot{V}O_2$ during recovery and subtracting the expected cumulative resting $\dot{V}O_2$ for the same period. The expected cumulative resting $\dot{V}O_2$ was calculated by multiplying the average preexercise resting $\dot{V}O_2$ during the final 2 min of rest by the duration of the recovery period (Fig. 2).

Lactate and methemoglobin. Blood samples were drawn into heparinized syringes during the resting period just before exercise began, during the final 30 s of each constant work rate exercise period and after 3 min of recovery. Samples were held on ice for no more than 20 min before analysis. Plasma lactate was measured using a rapid analyzer (Yellow Springs Instrument Co., Yellow Springs, Ohio). We determined the coefficient of variation for the assay to be 2.4%. Methemoglobin concentration was measured in whole blood using a CO-Oximeter (Instrumentation Laboratories, Lexington, Massachusetts).

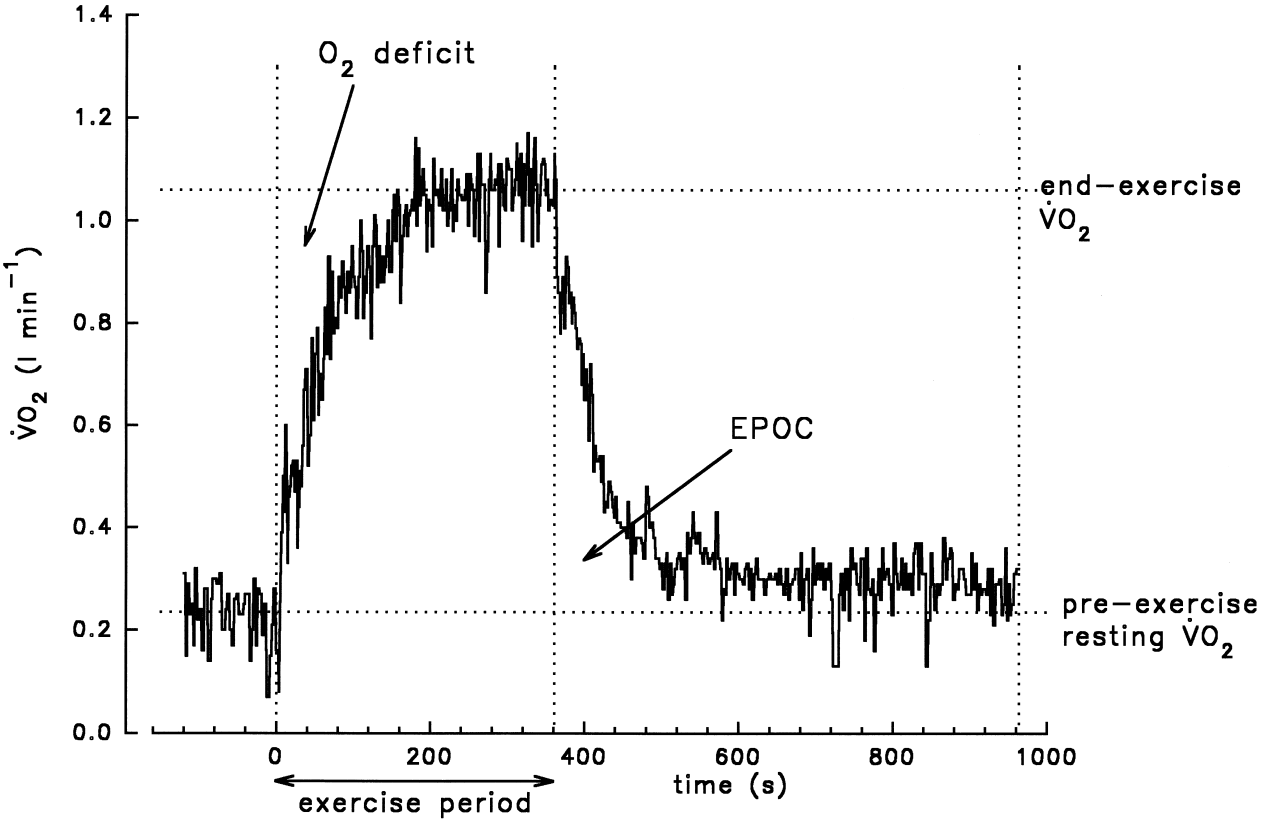

Figure 2. Illustration of the calculation of O_2 deficit and EPOC in a patient with PPH. Excess postexercise oxygen consumption (EPOC) was calculated for a recovery period of 10 min.

Other statistical analyses. Differences among groups were assessed using one-way analysis of variance (ANOVA) (Table 3) and two-way ANOVA with repeated measures (Table 2). Post-hoc significance testing was performed using the Tukey correction. With the two-way ANOVA, groups were compared at each time point if the interaction was significant. Relationships between variables were assessed by computing the correlation coefficient (r), and, where appropriate, by regression analysis performed using the least-squares method. The level of statistical significance was taken as 0.05 throughout.

RESULTS

There were no adverse events during exercise and all tests were completed according to the protocol.

Incremental test. Peak exercise work rate, $\dot{V}O_{2max}$ and the LAT were markedly lower in the patients than in the normals (Table 1).

Constant work rate tests. There was no significant rise in methemoglobin concentration in the patients after breathing the NO mixture (before NO, 0.46 ± 0.36%; at end of NO study, 0.54 ± 0.41%). Right ventricular systolic pressure was elevated in all PPH patients at rest. After breathing NO at 20 ppm for 15 min at rest, there was a modest fall from 83.8 ± 16.9 to 73.9 ± 21.6 mm Hg, $p < 0.01$ (two-way ANOVA with Tukey correction). No significant change in RVSP was observed in the control study breathing air (from 88.0 ± 20.8 to 86.7 ± 20.6 mm Hg).

Responses to exercise are shown in Tables 2 and 3. Marked differences were observed between the normal subjects and the patients with PPH. Within the PPH patients, however, gas exchange responses did not differ significantly between those experiments breathing air and those breathing NO. There was a small decrease in heart rate and increase in O_2 pulse with NO breathing (Table 2) compared with air breathing, but the differences did not achieve statistical significance.

The patients indicated much higher scores of perceived exertion than the normal subjects. Heart rate, $\dot{V}E$, $\dot{V}CO_2$, O_2 pulse and the respiratory exchange ratio (R) at the end of the exercise bout were also much greater in the patients. There was a trend towards an increased resting $\dot{V}O_2$ in the patient group compared with the normal subjects. However, $\dot{V}O_2$ was similar in patients and normal subjects at the end of the exercise period. By 3 min of recovery, $\dot{V}O_2$ had returned to resting values in the normal subjects, but not in the patients. There was a fall in oxyhemoglobin saturation in the PPH patients but not in the normal subjects. End-tidal O_2 was higher and end-tidal CO_2 was lower in patients at the end of exercise than at rest, while the converse was true in the normal subjects (Table 2).

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Table 2. Gas Exchange and Hemodynamic Variables After Breathing the Test Gas Mixture at Rest, at the End of the 6-Minute Exercise Period and After 3 Minutes of Resting Recovery

		Normals (Air)	PPH Air	PPH NO
Borg score	end	1.4 ± 0.9	4.8 ± 1.8‡	5.1 ± 2.2‡
$\dot{V}O_2$ (liters/min)	rest	0.28 ± 0.06	0.32 ± 0.09	0.35 ± 0.12‡
	end	0.97 ± 0.20†	0.94 ± 0.20†	0.96 ± 0.20†
	rec	0.27 ± 0.04	0.39 ± 0.08*§	0.40 ± 0.10§
$\dot{V}CO_2$ (liters/min)	rest	0.24 ± 0.05	0.28 ± 0.08	0.30 ± 0.10
	end	0.86 ± 0.23†	0.96 ± 0.21†	0.99 ± 0.19†‡
	rec	0.26 ± 0.03	0.42 ± 0.09†§	0.41 ± 0.11†§
Heart rate (beats/min)	rest	79 ± 15	92 ± 13§	89 ± 16‡
	end	108 ± 19†	132 ± 12†§	130 ± 15†§
	rec	81 ± 17	101 ± 13§	97 ± 17§
O_2 pulse (ml/beat)	rest	3.8 ± 1.5	3.5 ± 1.0	3.9 ± 1.3
	end	9.4 ± 3.1†	7.2 ± 1.5†‡	7.5 ± 1.5†‡
	rec	3.6 ± 1.3	3.9 ± 0.8	4.1 ± 0.9
R	rest	0.92 ± 0.057	0.87 ± 0.11	0.86 ± 0.07
	end	0.92 ± 0.10	1.03 ± 0.07†§	1.04 ± 0.05†§
	rec	1.00 ± 0.09*	1.08 ± 0.13†	1.04 ± 0.10†
Venous lactate (plasma; mmol/liter)	rest		1.5 ± 0.8	1.0 ± 0.3
	end		2.7 ± 1.3†	2.2 ± 1.1†
	rec		2.6 ± 1.2†	2.4 ± 1.0†
$\dot{V}E$ (liters/min)	rest	11.9 ± 2.4	14.3 ± 3.0	14.7 ± 4.3
	end	28.9 ± 5.1†	43.1 ± 7.0†§	45.5 ± 8.3†§
	rec	13.0 ± 1.8	20.2 ± 2.2†§	19.7 ± 3.4*§
Respiratory rate (per min)	rest	15.1 ± 3.7	18.4 ± 4.3	17.7 ± 4.0
	end	20.6 ± 6.1	28.5 ± 5.2†§	30.2 ± 6.5†§
	rec	15.3 ± 4.6	21.0 ± 5.0‡	18.6 ± 3.6
$\dot{V}E/\dot{V}CO_2$	rest	47.4 ± 8.3	53.1 ± 8.5	50.6 ± 8.3
	end	32.7 ± 3.5†	45.5 ± 7.3*§	46.7 ± 10.0§
	rec	48.3 ± 6.6	49.3 ± 6.7	48.9 ± 7.2
$\dot{V}E/\dot{V}O_2$	rest	43.4 ± 7.4	45.5 ± 7.3	43.3 ± 7.3
	end	30.1 ± 4.2†	46.5 ± 7.2§	48.3 ± 10.8§
	rec	48.3 ± 6.3	52.7 ± 6.7*	50.5 ± 6.2*
End-tidal CO_2 (mm Hg)	rest	36.8 ± 3.2	30.7 ± 3.6§	30.9 ± 4.3§
	end	42.9 ± 2.6†	29.3 ± 4.5§	28.7 ± 5.4§
	rec	37.8 ± 2.1	30.2 ± 3.1§	30.7 ± 3.4§
End-tidal O_2 (mm Hg)	rest	101.4 ± 4.6	108.6 ± 6.1§	108.2 ± 5.8§
	end	95.4 ± 5.9†	113.6 ± 5.3*§	114.6 ± 5.5†§
	rec	103.3 ± 2.7	114.2 ± 2.6*§	113.3 ± 2.1*§
S_pO_2 (%)	rest	94.2 ± 2.3 (n = 6)	95.3 ± 2.1	93.0 ± 2.2
	end	95.3 ± 2.1 (n = 6)	89.9 ± 4.1†§	87.9 ± 4.8†§
	rec	95.7 ± 1.8 (n = 6)	96.2 ± 2.9	94.3 ± 1.9

Data are mean ± SD. *$p < 0.05$. †$p < 0.01$ vs. corresponding rest value. ‡$p < 0.05$. §$p < 0.01$ vs. value in normals at same time-point, two-way analysis of variance with Tukey test.

NO = nitric oxide; PPH = primary pulmonary hypertension; R = respiratory exchange ratio ($\dot{V}CO_2/\dot{V}O_2$); S_pO_2 = hemoglobin saturation measured by pulse oximetry; $\dot{V}E$ = minute ventilation; $\dot{V}CO_2$ = minute carbon dioxide production; $\dot{V}O_2$ = minute oxygen consumption.

Analysis of kinetics, O_2 deficit and EPOC. Substantial intergroup differences were observed in the kinetics of $\dot{V}O_2$ increase in response to exercise (Table 3). In normal subjects, there was a rapid increase in $\dot{V}O_2$ at the onset of exercise, with early achievement of a plateau. In contrast, in PPH patients, $\dot{V}O_2$ rose slowly and in most patients did not appear to reach a plateau before the termination of exercise. Fitting of the single exponential model to the $\dot{V}O_2$ data resulted in a much longer τ and MRT in the patients than in the normal subjects, although the amplitude of the response was similar in both groups (Table 3). The recovery curve-fits also demonstrated much slower kinetics in the patients than in the normal subjects. The time delay before commencement of the exponential function in the recovery process was longer in the patients than in the normal subjects. The τ and MRT values obtained for exercise were similar to those for recovery (Table 3). In addition, there was a significant overall correlation between the τ values for exercise and recovery ($r = 0.68$, $p < 0.0001$) and between the MRT values for exercise and recovery ($r = 0.73$, $p < 0.0001$). Both O_2 deficit and EPOC were greater in the patients than in the normal subjects (Table 3). In both groups, the EPOC after 10 min was significantly greater than the corresponding O_2 deficit, but there was a significant positive correlation between the two variables (Fig. 3).

The kinetics of heart rate increase and decrease with exercise and recovery were qualitatively similar to the $\dot{V}O_2$ responses. There was no significant intergroup difference in the speed of rise of $\dot{V}CO_2$ during exercise,

Table 3. Curve-fit Parameters of the $\dot{V}O_2$, $\dot{V}CO_2$ and Heart Rate Responses and O_2 Deficit and EPOC During Exercise and Recovery in Normal Subjects and Patients with PPH Breathing Air and Air Supplemented With NO 20 ppm

	Normals (Air)	PPH Air	PPH NO
Exercise			
$\dot{V}O_2$			
c (liters/min)	0.30 ± 0.05	0.35 ± 0.09	0.34 ± 0.09
td (s)	2.90 ± 6.65	1.18 ± 2.98	3.54 ± 5.08
A (liters/min)	0.65 ± 0.16	0.61 ± 0.14	0.61 ± 0.13
τ (s)	29.83 ± 15.58	61.99 ± 13.59†	58.06 ± 15.66†
MRT (s)	32.73 ± 14.79	63.17 ± 14.99†	61.60 ± 15.45†
O_2 deficit (liters)	0.34 ± 0.22	0.73 ± 0.21†	0.72 ± 0.23†
$\dot{V}CO_2$			
c (liters/min)	0.27 ± 0.03	0.30 ± 0.09	0.29 ± 0.07
td (s)	2.7 ± 6.8	4.0 ± 7.3	3.7 ± 4.8
A (liters/min)	0.63 ± 0.17	0.71 ± 0.19	0.73 ± 0.18*
τ (s)	64.0 ± 42.5	73.7 ± 20.8	75.0 ± 31.5
MRT (s)	66.7 ± 41.0	77.7 ± 22.6	78.7 ± 32.8
Heart rate			
c (beats/min)	79 ± 15	93 ± 13	89 ± 15
td (s)	2.4 ± 2.2	0.0 ± 0.0	1.5 ± 3.3
A (beats/min)	28 ± 6	40 ± 13*	41 ± 13
τ (s)	22.3 ± 21.0	79.5 ± 38.4*	87.1 ± 55.5†
MRT (s)	24.7 ± 19.4	79.5 ± 38.4†	88.6 ± 54.7†
Recovery			
$\dot{V}O_2$			
c (liters/min)	0.27 ± 0.04	0.35 ± 0.08†	0.35 ± 0.09†
td (s)	−0.42 ± 3.68	16.98 ± 11.44†	15.98 ± 13.54†
A (liters/min)	0.69 ± 0.17	0.62 ± 0.15	0.61 ± 0.14*
τ (s)	34.17 ± 8.55	65.52 ± 26.53†	57.38 ± 6.71*
MRT (s)	34.59 ± 7.11	82.50 ± 29.94†	73.36 ± 15.87†
EPOC at 10 min (liters)	0.52 ± 0.18	0.98 ± 0.22†	0.96 ± 0.20†
$\dot{V}CO_2$			
c (liters/min)	0.25 ± 0.04	0.31 ± 0.07†	0.31 ± 0.07†
td (s)	0.0 ± 6.0	2.5 ± 5.3	7.8 ± 13.8
A (liters/min)	0.64 ± 0.18	0.69 ± 0.17	0.68 ± 0.15
τ (s)	46.2 ± 16.6	100.5 ± 24.6*	75.0 ± 32.0
MRT (s)	46.2 ± 16.6	100.5 ± 24.6†	82.7 ± 24.5†
Heart rate			
c (beats/min)	81 ± 16	98 ± 13*	94 ± 17
td (s)	5.7 ± 6.5	16.8 ± 17.5	17.3 ± 12.9
A (beats/min)	27 ± 7	36 ± 12	35 ± 12
τ (s)	16.3 ± 12.1	69.6 ± 36.5†	58.1 ± 28.1†
MRT (s)	22.0 ± 9.0	86.4 ± 37.3†	75.4 ± 26.5†

Data are mean ± SD. *$p < 0.05$. †$p < 0.01$ vs. normals, analysis of variance with Tukey test.

Curve-fit parameters: c = baseline value; td = time delay before commencement of exponential component; A = amplitude of response; τ = time constant of exponential response; MRT = mean response time (MRT = td + τ); EPOC = excess postexercise oxygen consumption; NO = nitric oxide; PPH = primary pulmonary hypertension; $\dot{V}CO_2$ = minute carbon dioxide production; $\dot{V}O_2$ = minute oxygen consumption.

although the amplitude of the response was greater in the patients than the normal subjects. During recovery, $\dot{V}CO_2$ fell more slowly in the patients than in the normal subjects (Table 3).

DISCUSSION

We have demonstrated marked differences between patients with PPH and normal subjects in their responses to the same absolute constant work rate exercise. At the end of the exercise bout, the patients had much greater physiological stress than the normal subjects, as shown by their higher heart rate, lower O_2 pulse and higher respiratory exchange ratio (Table 2). The $\dot{V}O_2$ at the end of exercise was similar in the two groups, but this was achieved much more slowly in the patients than in the normal subjects. This is quantified by the curve-fit parameters, with patients having a similar amplitude of response to normal subjects, but a much longer exponential time constant. The inhalation of NO in the PPH patients caused a modest, but significant, fall in RVSP gradient at rest. The apparent hemodynamic improvement was not translated into any significant change in exercise response.

Physiological stress. An abnormally elevated heart rate and depressed O_2 pulse in response to a given absolute work rate characteristically occur in subjects with circulatory disease or deconditioning (3,21). Low stroke volume is

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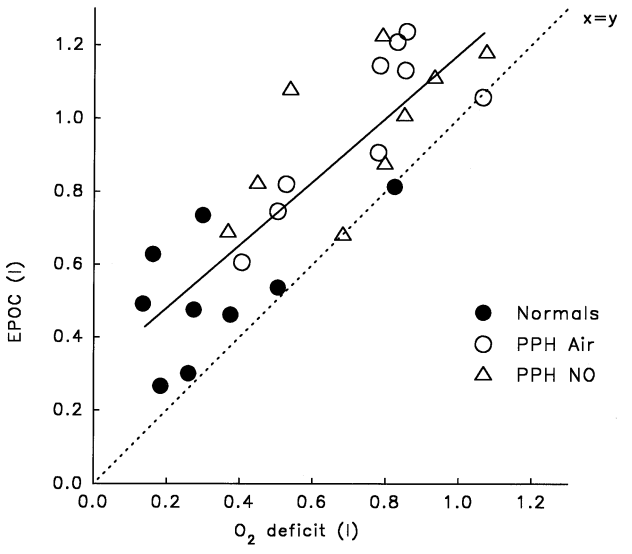

Figure 3. Excess postexercise oxygen consumption (EPOC) plotted as a function of O_2 deficit in PPH patients breathing air and breathing NO and in normals breathing air. The line of identity is shown by the dashed line. The combined line of regression is illustrated by the solid line. (EPOC = 0.87(O_2 deficit) + 0.31, r = 0.84, $p < 0.0001$).

probably the main factor responsible. Stroke volume is abnormally low in PPH and fails to increase with exercise (22). In PPH (23) and chronic heart failure (24,25), the systemic extraction of O_2 during exercise is at least as efficient as in normals. In contrast to chronic heart failure (26), however, we found reduced S_pO_2 levels in our patients with PPH. This desaturation could have resulted in a reduced arteriovenous O_2 difference, although we did not measure mixed venous or femoral O_2 content. Slightly higher hemoglobin concentrations in the patients than in the normal subjects (Table 1) may have partially compensated for the arterial desaturation.

The respiratory exchange ratio (R) at peak exercise was much greater in the PPH patients than the normal subjects, and suggests an increased reliance on carbohydrate as a substrate in skeletal muscle and/or increased buffering of lactic acid by bicarbonate (27). It is unlikely to be accounted for by hyperventilation, because end-tidal CO_2 did not decrease from resting values during exercise. The work rate performed was much greater as a proportion of maximal work rate in the patients than in the normal subjects. As relative work rate increases, whole-body R tends to increase reflecting an increase in overall carbohydrate oxidation and a decrease in lipid oxidation (27,28). However, aerobic metabolism alone cannot lead to an R of >1.0. Because R was >1.0 at the end of exercise in the PPH patients, this implies that ongoing buffering of lactic acid was also significant and that a true steady-state had not been achieved (29).

Minute ventilation was greater in the PPH patients than in the normals at the end of exercise. This was accompanied by greater ventilatory equivalents for O_2 and CO_2, and by lower end-tidal CO_2 and greater end-tidal O_2. Taken together with the fall in S_pO_2 in the PPH patients, these findings imply decreased ventilatory efficiency. Several factors may account for this increased ventilatory response (30). 1) To compensate for an impaired right ventricular output response, a lactic acidosis would develop at a low work rate. This would drive ventilation and reduce the arterial CO_2 set-point. In turn, a greater $\dot{V}E$ is necessary to achieve the same $\dot{V}CO_2$. The partial pressure of CO_2 in arterial blood has been shown to be low in PPH (2). 2) Shunting of pulmonary arterial blood may occur, either through a patent foramen ovale or intrapulmonary channels. Dantzker and colleagues (31) applied the multiple inert gas technique to a group of patients with chronic obliterative pulmonary hypertension and found variable increases in veno-arterial shunt at rest, with values ranging from 4% to 24% of cardiac output. Such right-left shunting would result in a fall in the partial pressure of O_2 in arterial blood and stimulate the carotid chemoreceptors, resulting in increased ventilatory drive. Our patient with the proven patent foramen ovale had the most marked fall in S_pO_2. 3) A true increase in physiological dead space/tidal volume ratio could occur because the underlying disease reduces perfusion to ventilated lung. Thus, particularly during exercise, when new capillary bed is normally recruited, acini may remain underperfused in PPH.

Kinetic responses. The kinetics of change in $\dot{V}O_2$ with onset of exercise were much slower in the PPH patients than in the normal subjects. From the Fick equation, this implies that cardiac output and/or arteriovenous O_2 difference increased at a slower rate in the patients than in the normal subjects. We know of no studies that have examined the dynamics of either of these components invasively in PPH. However, the elevated pulmonary arterial resistance in PPH appears to constrain the increase in cardiac output with exercise (22). Additionally, as discussed above, peripheral O_2 extraction appears normal, or even excessive in PPH, with very low mixed venous O_2 saturation being observed during exercise (23). These observations would favor cardiac output limitation as the cause for the slow kinetics. Our finding of slowed heart rate kinetics in PPH is also consistent with the view that the abnormal cardiac output response is primarily responsible for the slow rise in $\dot{V}O_2$. In the absence of continuous measurements of arteriovenous O_2 difference, we cannot exclude peripheral abnormalities as a factor in the delayed $\dot{V}O_2$ kinetics in PPH. In chronic heart failure, skeletal muscle abnormalities occur, including reduced mitochondrial density and aerobic enzyme capacity (32). If similar changes were present in PPH, they could contribute to the slow rise in $\dot{V}O_2$.

The time course of the recovery process was also prolonged in PPH and there was a close correlation between the kinetics of the exercise and recovery $\dot{V}O_2$. These observations suggest that the factors governing the rise in $\dot{V}O_2$ with exercise, as discussed above, are closely related to those controlling its decline during recovery. The relationship between exercise and recovery kinetics is mirrored in

the relationship between O_2 deficit and EPOC (Fig. 3). In the PPH patients, there was a longer time delay before commencement of the exponential phase of declining $\dot{V}O_2$ during recovery than in the normal subjects. This may represent a period during which the $\dot{V}O_2$ appropriate to the intracellular state is greater than can be delivered by the circulation.

The kinetics of the increase in $\dot{V}CO_2$ with exercise were not significantly different in the PPH patients compared with the normal subjects, but the decrease during recovery was much slower in the patients. Buffering of increased amounts of lactic acid early during exercise is likely to have resulted in the augmentation of CO_2 produced by the slowly increasing aerobic mechanisms in the patients. Conversely, during recovery, persistent acidosis could have accounted for the continuing production of buffer CO_2, thus prolonging further the slow decline in $\dot{V}CO_2$ attributable to aerobic processes.

Oxygen deficit and EPOC. The O_2 deficit incurred during the exercise bout was greater in patients than in normal subjects. This is a direct consequence of the slower $\dot{V}O_2$ kinetics in the patients, because the $\dot{V}O_2$ at the end of exercise was similar in both groups, and the resting $\dot{V}O_2$, if anything, was slightly greater in patients. Magnetic resonance spectroscopy studies in chronic heart failure patients suggest that ATP and phosphocreatine (PCr) depletion are greater than in normal subjects at the same absolute exercise intensity (33). If the same biochemical abnormalities are present in PPH, this implies that the large O_2 deficit is associated with similar excess depletion of high-energy compounds. The EPOC after 10 min of recovery was also greater in the patients than in the normal subjects. While the EPOC was systematically greater than the O_2 deficit, there was nonetheless a significant positive correlation. During early recovery, postexercise $\dot{V}O_2$ and resynthesis of PCr have been found to follow a similar time course (34). This suggests that the early phase of EPOC is due to PCr repletion, and our finding of a correlation between EPOC and O_2 deficit is consistent with this hypothesis. Restoration of oxyhemoglobin saturation to resting levels in PPH is also likely to contribute to the significantly increased EPOC.

In normal subjects, when EPOC is measured over periods of an hour or more, there appears to be little relationship between it and the O_2 deficit. After the early recovery period, other factors, such as elevated catecholamines, fatty acids and temperature, may become important in the causation of the EPOC (8). These factors probably bear a less direct relationship than PCr depletion to the conditions of the preceding exercise bout.

In calculating the O_2 deficit, we have assumed that the end-exercise $\dot{V}O_2$ is the $\dot{V}O_2$ appropriate to the work rate being performed. However, during heavy constant work rate exercise, it is known that the $\dot{V}O_2$ does not reach a steady-state before the end of exercise (35). It is likely that this situation pertained in our PPH patients. For this reason, the end-exercise $\dot{V}O_2$ may be a slight underestimate of the $\dot{V}O_2$ appropriate to the work rate in the PPH patients. It follows that our estimation of O_2 deficit is likely to be somewhat low in the patients.

Effect of NO. We were unable to demonstrate a change in any of the exercise responses with NO breathing, despite a modest reduction in RVSP at rest. As all patients remained on their usual medications, any positive effect of NO is likely to have been less than if NO had been administered alone. In addition, we did not obtain Doppler estimations of RVSP during exercise or measure hemodynamics directly. We cannot be certain that NO improved pulmonary vascular resistance or cardiac output during exercise.

Summary. Severe gas exchange abnormalities occur during exercise and recovery in patients with PPH. In particular, there is slowing of $\dot{V}O_2$ kinetics with excessive O_2 deficit and EPOC. These abnormalities persist despite a modest acute improvement in RVSP gradient resulting from NO inhalation.

Acknowledgments

We wish to thank Dr. N. Qi and Dr. T. Cao for performing the echocardiographic measurements. We are very grateful to Joy Beckman, RN for her great help in patient recruitment and care, and to Dr. C.C. Patterson for his statistical advice.

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